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Preliminary communication

Do venlafaxine XR and paroxetine equally influence negative and positive affect?

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Abstract

Background: We assessed the therapeutic effects of venlafaxine XR and paroxetine on mood and anxiety symptoms derived from the tripartite model of mood. We hypothesized that the two antidepressants would have largely similar effects on symptoms of negative affect because both agents influence serotonergic systems. However, based on evidence indicating linkages between catecholaminergic activity and the emotional dimension of positive affect, we hypothesized that the catecholaminergic effects of venlafaxine XR would yield particularly pronounced effects on symptoms of positive affect.
Methods: Twenty depressed outpatients were randomly assigned to treatment with either venlafaxine XR (225 mg/day) or paroxetine (30 mg/day) during a 12-week treatment trial. Weekly mood ratings were collected using the Mood and Anxiety Symptom Questionnaire [Watson, D., Clark, L.A., Weber, K., Assenheimer, J.S., Strauss, M.E., McCormick, R.A., 1995. Testing a tripartite model: II. Exploring the symptom structure of anxiety and depression in student, adult, and patient samples. J. Abnorm. Psychol. 104 (1), 15–25] [Watson, D., Weber, K., Assenheimer, J.S., Clark, L.A., Strauss, M.E., McCormick, R.A., 1995. Testing a tripartite model: I. Evaluating the convergent and discriminant validity of anxiety and depression symptom scales. J. Abnorm. Psychol. 104 (1), 3–14].
Results: Consistent with predictions, analyses revealed that there were no significant differences between venlafaxine XR and paroxetine on measures of negative affect. However, contrary to predictions, the two medications produced similar changes on measures of positive affect.
Limitations: Replication and extension using a larger sample size are mandated.
Conclusions: These preliminary results suggest that two antidepressants that appear to have dissimilar mechanisms of action may nevertheless have similar effects on the positive and negative affective components of depression. Alternatively, paroxetine may have a clinically relevant noradrenergic effect at the dose tested.

Keywords: Depression; Anhedonia; Venlafaxine XR; Paroxetine; Tripartite model

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1. Introduction

We have recently proposed that a given antidepressant medication may produce a distinct profile of change across different symptom dimensions depending on its fundamental mechanisms of action (Shelton and Tomarken, 2001; Tomarken et al., 2004). In the current investigation, we assessed the effects of different antidepressant agents on symptoms of depression and anxiety derived from the tripartite model of mood disorders (e.g., Clark and Watson, 1991; Watson et al., 1995a,b). This model posits that symptoms of general distress are common to both mood and anxiety disorders, while symptoms of anhedonia are relatively specific to depression. A third dimension of somatic anxiety is primarily linked to panic disorder and perhaps other types of anxiety disorders. Watson et al., (1995a,b) have developed and validated a self-report measure, the Mood and Anxiety Symptoms Questionnaire (MASQ), which assesses these dimensions of mood.

Paroxetine, a selective serotonin reuptake inhibitor (SSRI), has a notably higher affinity for the serotonin transporter than for the norepinephrine transporter, and it demonstrates insignificant binding to postsynaptic receptors of any class (Owens et al., 1997; Reist et al., 1996). Previous findings suggest that drugs that enhance serotonin transmission such as paroxetine have a more profound effect on symptoms of negative affect than symptoms of positive affect (e.g., Bodkin et al., 1997; Knutson et al., 1998; Reist et al., 1996; Shelton and Brown, 2000; Shelton and Tomarken, 2001; van Praag et al., 1987). This evidence suggests that serotonergic agents are more likely to lower subjective anxiety and tension than relieve anhedonia. Based on these findings, we predicted that paroxetine would have stronger effects on general distress than on anhedonia.

Conversely, agents that modulate catecholaminergic activity tend to elevate forebrain dopamine activity (e.g., Karson et al., 1983) and thus increase positive affect (e.g., Depue and Collins, 1999; Depue et al., 1994). Furthermore, antidepressants with catecholaminergic mechanisms of actions have been shown to increase positive affect in individuals with depression (e.g., Bodkin et al., 1997; Tomarken et al., 2004). Venlafaxine XR is a novel antidepressant with proven efficacy for treating depression (e.g., Rudolph, 2002; Stahl et al., 2002; Thase et al., 2001). It inhibits the reuptake of serotonin, norepinephrine, and, to a lesser degree, dopamine (Muth et al., 1986), and repeated exposure increases the responsiveness of noradrenergic and dopaminergic systems (Maj and Rogoz, 1999). Because of the link between catecholaminergic transmission and positive affect, we hypothesized that venlafaxine XR would produce relatively greater decreases in anhedonic symptoms than paroxetine. We also hypothesized that the two agents would have comparable effects on negative affect because both enhance serotonin transmission. We tested these hypotheses by assessing weekly self-reported mood changes during a 12-week treatment study.

2. Method

Written informed consent was obtained from all participants. Participants were adult outpatients who met DSM-IV (American Psychiatric Association, 1994) criteria for major depression as determined by the Structured Clinical Interview for DSM-IV—patient version (First et al., 1997). Participants were recruited from advertisements and referrals by physicians at the Vanderbilt University Medical Center Department of Adult Psychiatry. Participants: (1) had scores on the 17-item version of the Hamilton Rating Scale for Depression (Hamilton, 1960) that were greater than 17; (2) were free of benzodiazepines for at least 2 weeks prior to their baseline assessment, antidepressant medication for at least 3 weeks prior to their baseline assessment, and fluoxetine, antipsychotics, lithium, carbamazepine, or valproate for at least 5 weeks prior to their baseline assessment; and (3) did not have: (a) any clinically significant physical illness that would limit treatment with either study drug; (b) a history of bipolar affective disorder; (c) any history of a psychotic Axis I disorder, including major depression with psychotic features; (d) current predominant nonpsychotic Axis I disorder, antisocial, borderline, or schizotypal Axis II personality disorders; (e) subnormal intellectual potential; (f) a history of substance abuse in the past 6 months or substance dependence in the past 12 months; (g) a known hypersensitivity to either study drug; or (h) any history of a seizure disorder.

Twenty-four outpatients were screened for study participation. Four did not meet criteria for randomization. The remaining 20 participants were randomly assigned to receive either venlafaxine XR (n=10; age range: 27.3–54.5 years, mean (S.D.)=42.6 (9.2), 6 women) or paroxetine (n=10; age range: 22.2–50.2 years, mean (S.D.)=37.6 (9.0), 7 women) for 12 weeks. Patient groups did not differ with respect to age [$t(18)=1.23$, $p>0.20$] or gender [$\chi^2(1)=0.22$, $p>0.60$]. Below, the two groups of patients will be denoted VEN and PAR.

Mood data were first collected at an initial screening visit (i.e., week 0) when participants had not yet been assigned to medication groups. At the next clinic visit (i.e., week 1), participants completed all measures again and then were randomly assigned to treatment with either VEN or PAR for 12 weeks (i.e., weeks 2–13) in an open-label fashion. All study evaluators were unaware of participant group membership. VEN was started at 37.5 mg/day and was advanced by 75 mg/day weekly steps to 225 mg/day as tolerated, and all participants achieved a dose of 225 mg/day by the week 8 visit. Participants in the PAR group were started at 10 mg/day, were increased to 20 mg/day in week 3, and to 30 mg/day from weeks 4 to 13. One participant in the PAR group did not achieve 30 mg/day until week 5. Another participant in the PAR group was dropped to 20 mg/day for weeks 7 and 8 and then increased back to 30 mg/day.

Participants completed all measures on a weekly basis. The primary dependent measures were the Clinical Global Impressions Scale (CGI; "Clinical Global Impressions,"s 1976); the 90-item version of the Mood and Anxiety Symptom Questionnaire (Watson et al., 1995a,b); the 17-item version of the Hamilton Rating Scale for Depression (HAM-D-17; Hamilton, 1960); the Beck Depression Inventory, second version (BDI; Beck et al., 1996); the Hamilton Rating Scale for Anxiety (HAM-A; Hamilton, 1959); the Beck Anxiety Scale Anxiety (BAI; Beck et al., 1988); and a measure of adverse events.

The 90-item version of the MASQ contains five scales, four of which were theoretically relevant in the present study. The scales used were anhedonic depression (AD) and three measures that load on the higher-order dimension of generalized distress (GD): GD depressive symptoms (GDD), GD anxious symptoms (GDA), and GD mixed symptoms (GDM). The AD scale consists of negative (i.e., positively keyed) items indicative of the anhedonia/low positive affect pole, and positive (i.e., negatively keyed) items indicative of the high positive affect pole. In addition to the overall MASQ AD scale, we also present separate analyses of the two poles (e.g., Tomarken et al., 2004).

Random regression analyses were conducted to compare the two groups on all measures (Gibbons et al., 1993). We specified models that included fixed effect predictors of group, the linear effect of time, and the critical group×linear interaction that tested for group differences in patterns of change. SAS PROC MIXED was used for all analyses (e.g., Littell et al., 1996). As an additional analytic approach, we conducted analyses of covariance (ANCOVAs), with each participant's last nonmissing observation as the dependent variable (for 16 of 20 participants, this was week 13) and pretreatment (i.e., week 0) values as the covariate.

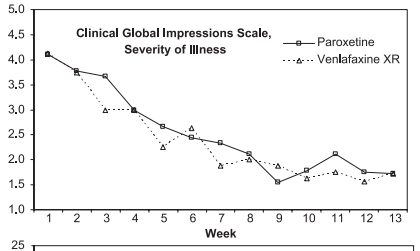
3. Results

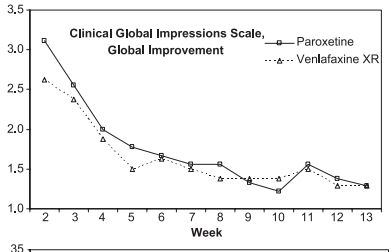
One male participant in the VEN group did not return after the third week. Additionally, two female participants, one each from the PAR and VEN groups, did not return for their last 2 weeks (i.e., completed through week 11), and one male participant in the PAR group did not return for his last week (i.e., completed through week 12).

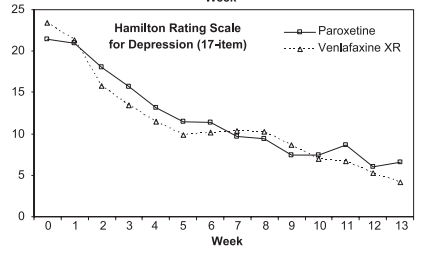
3.1. Treatment outcome analyses

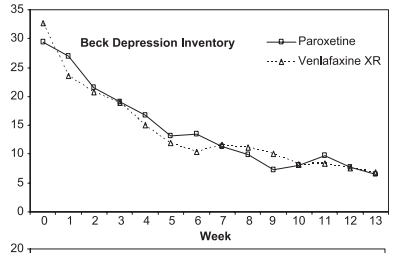
3.1.1. Random regression analyses

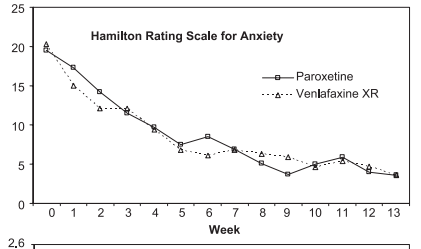
Fig. 1 displays changes over time for 12 of the primary measures. It is readily apparent from these graphs that: (1) over the full 12 weeks of treatment (i.e., weeks 2–13), both the VEN and PAR groups demonstrated notable reductions on all measures: and (2) the degree of change was very comparable across the two treatment groups. The results of random regression analyses indicated highly significant overall linear declines across all dependent measures (all $p<0.0005$; see Fig. 1). However, there were no significant group×linear interactions for any of the measures analyzed (all $p>0.12$). Given our a priori

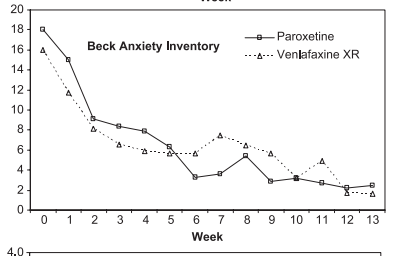

Clinical Global Impressions Scale,
Severity of Illness
Paroxetine
Venlafaxine XR
Week

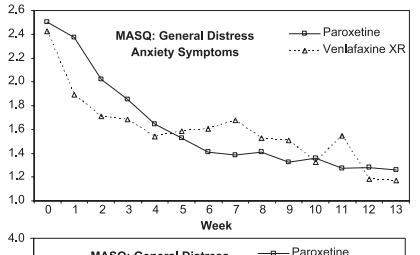

Clinical Global Impressions Scale,
Global Improvement
Paroxetine
Venlafaxine XR
Week

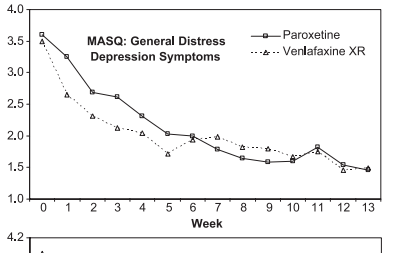

Hamilton Rating Scale
for Depression (17-item)
Paroxetine
Venlafaxine XR
Week

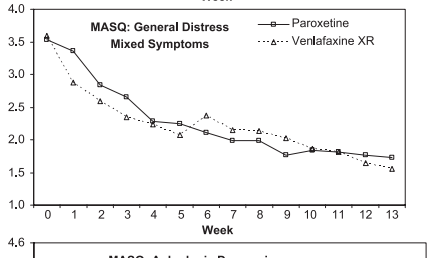

Beck Depression Inventory
Paroxetine
Venlafaxine XR
Week

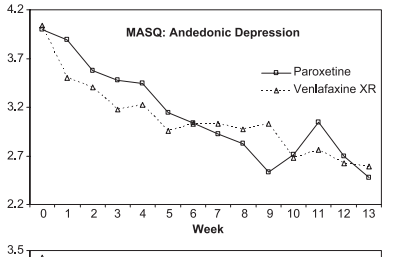

Hamilton Rating Scale for Anxiety
Paroxetine
Venlafaxine XR
Week

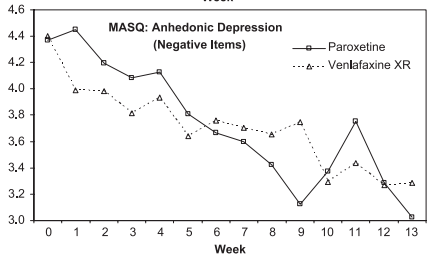

Beck Anxiety Inventory
Paroxetine
Venlafaxine XR
Week

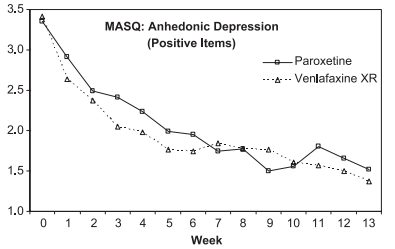

MASQ: General Distress
Anxiety Symptoms
Paroxetine
Venlafaxine XR
Week


MASQ: General Distress
Depression Symptoms
Paroxetine
Venlafaxine XR
Week


MASQ: General Distress
Mixed Symptoms
Paroxetine
Venlafaxine XR
Week


MASQ: Andedonic Depression
Paroxetine
Venlafaxine XR
Week


MASQ: Anhedonic Depression
(Negative Items)
Paroxetine
Venlafaxine XR
Week


MASQ: Anhedonic Depression
(Positive Items)
Paroxetine
Venlafaxine XR
Week

hypotheses, it is particularly noteworthy that there were no significant group×linear interactions for either pole of the MASQ AD scale or the overall AD scale (all $p>0.30$).

3.1.2. ANCOVA

Preliminary analyses indicated that groups did not significantly differ on pretreatment values (all $p>0.09$). The results of the ANCOVAs were consistent with the results of the random regression analyses: there were no statistically significant differences between groups on any of the mood and symptom measures (all $p>0.15$).

3.1.3. Adverse events

There were no differences between the two treatment groups on numbers of adverse events (VEN mean=4.8, S.D.=3.0, PAR mean=5.7, S.D.=3.0, $t(18)=0.67$, $p>0.50$).

4. Discussion

Venlafaxine XR and paroxetine produced robust changes on severity of illness, global improvement, and symptoms of depression and anxiety, as measured by self-report and clinical ratings. As expected, there were no between-group differences in the magnitude of change over time on measures of negative affect. However, contrary to predictions, there were no differences between treatment groups on measures of anhedonia and positive affect. The absence of significant differences on these measures runs contrary to our original hypothesis that the catecholaminergic effects of venlafaxine XR would produce more robust effects than paroxetine on the anhedonia/positive affect dimension of mood and symptoms.

One salient question is whether the failure to find effects on measures of anhedonia is due to low power resulting from small sample sizes. To address this issue, we computed measures of association that assess magnitude of effect and are less sensitive to sample sizes than statistical significance tests. An index that is applicable to random regression analyses is the proportional reduction in unexplained variability afforded by specific predictors. For the MASQ AD scale as a whole, as well as each pole of the MASQ AD scale, we computed the proportional reduction in the estimated random variability of the linear slopes due to the inclusion of the group×linear interaction terms in the statistical model (Bryk and Raudenbush, 1992). Across all three measures, our calculations indicated proportional reductions between 4% and 7%. Although certainly not conclusive, these calculations suggest relatively small differences between treatments on anhedonia rather than low power per se.

There are several possible explanations for the similar effects that we observed for the two treatments. One issue is the specificity of the antidepressant effects of the medications used. Perhaps paroxetine ultimately produced changes in noradrenergic or dopaminergic neurotransmission that were sufficient to produce effects on positive affect. For example, whereas the direct mechanism of antidepressant action of paroxetine primarily is inhibition of serotonin reuptake (e.g., Reist et al., 1996), serotonergic activity is known to modulate midbrain and forebrain dopaminergic systems (Depue and Spoont, 1986; Shelton and Brown, 2000; Zald and Depue, 2001). Additionally, several findings suggest the possibility that paroxetine can have meaningful noradrenergic effects (e.g., Gilmor et al., 2002; Owens et al., 1997). Although this notion is speculative, it could be that the norepinephrine transporter blockade induced by the 30-mg/day dosages used in the present study was minimally sufficient to induce measurable benefits on mood and symptom measures.

It is also possible that a tricyclic antidepressant, other medications (e.g., bupropion SR; Tomarken et al., 2004), or additional treatment components (e.g., sleep

Fig. 1. Weekly scores on Clinical Global Impressions Severity of Illness Scale (first row, left); Clinical Global Impressions Global Improvement Scale (first row, right); Hamilton Rating Scale for Depression (second row, left); Beck Depression Inventory (second row, right); Hamilton Rating Scale for Anxiety (third row, left); Beck Anxiety Inventory (third row, right); MASQ General Distress Anxiety Symptoms (fourth row, left); MASQ General Distress Depression Symptoms (fourth row, right); MASQ General Distress Mixed Symptoms (fifth row, left); MASQ Anhedonic Depression (fifth row, right); MASQ Anhedonic Depression Negative Items (sixth row, left, e.g., "withdrawn"); and MASQ Anhedonic Depression Positive Items (sixth row, right, e.g., "enthusiastic") for depressed outpatients who received either paroxetine or venlafaxine XR for 12 weeks. The Clinical Global Impressions Scale Severity of Illness Scale was not assessed at week 0 and the Clinical Global Impressions Global Improvement Scale was not assessed at weeks 0 and 1. The MASQ scales have ranges from 1 to 5.

deprivation; Tomarken et al., 1997) might have yielded stronger effects than VEN alone on measures of anhedonia. Moreover, it is important to recognize that, in the long run, a given antidepressant may have indirect effects on mood states that are broader than the effects directly attributable to its pharmacological mechanisms of action. For example, even if the serotonergic effects of paroxetine initially produce declines in general distress, such declines may enable a depressed individual to engage in more positive interpersonal interactions that could contribute to diminished anhedonia. Finally, the inclusion of a placebo group might have changed our results. It is conceivable that one, but not both, of the active treatment groups would have significantly differed from placebo. The strong similarity between the two treatment groups makes this unlikely, but it bears consideration in future studies.

Overall, our results indicate that both venlafaxine XR and paroxetine are effective antidepressants. Both have robust effects on symptoms of depression, anxiety, and anhedonia in a depressed outpatient sample. Because of the relatively small sample size in the current investigation, our findings would appear to mandate replication in a larger-scale study.

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